TRANSCUTANEOUS POSTERIOR TIBIAL NERVE STIMULATION (TPTNS) FOR TREATING PATIENTS WITH PREMATURE EJACULATION PHASE II CLINICAL TRIAL

CODE CLINICAL TRIALS NCT03204890

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ABSTRACT

Background: Transcutaneous posterior tibial nerve stimulation is an effective therapy for controlling urinary incontinence. Premature ejaculation (PE) and urinary incontinence are anatomically and physio-pathologically similar. Based on this, the use of this therapy is considered to be viable for the control of PE.

Objective: To evaluate the efficacy of transcutaneous posterior tibial nerve electrostimulation for the ejaculatory reflex.

Patients and Methods: Phase II clinical trial. Patients with a diagnosis of premature ejaculation who are treated at the Colombia Boston Medical Group clinic will be included. The participants will receive 3 transcutaneous posterior tibial nerve stimulation therapies per week for 12 weeks. The IELT and the PEDT scale will be evaluated on week 6, at the end of treatment and three months after completing the protocol.

Expected Impact: Generate scientific knowledge about the efficacy of a new option to treat premature ejaculation, which can subsequently be compared with current treatments.

INTRODUCTION

Premature ejaculation is a male sexual dysfunction defined by the WHO as “an inability to delay ejaculation sufficiently to enjoy intercourse,” and defined by the ISSM as “ejaculation which always or nearly always occurs prior to or within one minute of vaginal penetration, which the patient is unable to control and which causes distress or depression in the patient or the partner.” This sexual health problem affects a large number of men, with a total prevalence of 22.7% (1).

Different treatment modalities exist for this condition. According to the European Urology Society’s guide for treating sexual dysfunctions, the principal treatment is medication that regulates the reuptake of neurotransmitters such as serotonin, in addition to behavioral and psychological therapy.

Transcutaneous posterior tibial nerve stimulation is a therapy which pelvic-perineal therapists have recently used to treat a variety of pelvic floor disorders, including urge urinary incontinence and chronic pelvic pain. Favorable results have been observed and this can be used as an alternative when medications are not effective. (2,3)

Based on the results from neuro-stimulation of the posterior tibial nerve for a variety of pelvic pathologies (4,6), and given the physiology and neuroanatomy of these structures, the use of this therapy for patients with premature ejaculation may inhibit the parasympathetic function of this reflex, which primarily affects the expulsion stage of ejaculation. In addition, since these stages are regulated by the autonomic nervous system and are linked with it, the sympathetic effect of emission could also be affected by producing a global delay in the start of the ejaculatory reflex.

Our research is therefore interested in identifying whether the application of this therapeutic modality has beneficial effects on the treatment of primary premature ejaculation, where delaying intravaginal ejaculation latency time (IELT) is an indicator of the success of the proposed treatment and protocol.

THEORETICAL FRAMEWORK

The diagnosis of premature ejaculation is entirely clinical and depends on the ability of the clinician to determine whether the criteria are met, based on different definitions that exist for the study of this dysfunction. Some of the most important are:

1- DSM 5 Diagnostic and Statistical Manual by the American Psychiatric Society:

A- A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately one minute following vaginal penetration and before the person wishes it.

B- The symptoms in criterion A have been present for at least six months and experienced on almost all or all (approximately 75% to 100 %) occasions of sexual activity.

C- The symptoms in criterion A produce clinically significant distress in the individual.

D- The sexual dysfunction is not better explained by a non-sexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

2-American Urology Association:
Ejaculation that occurs before or shortly after penetration, causing distress to either one or both partners.

3-WHO (World Health Organization):
Inability to delay ejaculation sufficiently to enjoy sexual intercourse.

4-International Society of Sexual Medicine
Ejaculation occurring prior to or within one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences.

Premature ejaculation can be classified as primary or secondary. In the former, ejaculation always or nearly always occurs around one minute after vaginal penetration or sooner, it has a genetic origin (7) and is caused by changes in the levels of diverse neurotransmitters in the central nervous system, serotonin in particular (8,9). It is present since the beginning of sexual life. Secondary premature ejaculation appears after having had satisfactory sexual performance for several years.

Current treatment for premature ejaculation is primarily based on its physiopathology at the level of the nervous system, with regulation of serotonin levels being the primary objective. To this end, certain groups of medications are used that act on the central nervous system by increasing serotonin in certain receptors that regulate the ejaculatory reflex. Thus, the most commonly used medications are tricyclic antidepressants and selective and non-selective inhibitors of serotonin uptake. These have shown good results which multiple studies have confirmed for over several years. Those most commonly used are Clomipramine, Paroxetine, Sertraline and Dapoxetine. (10,11)

Another group of medications used with good results is opioid analgesics, such as Tramadol, that act on serotonin receptors and also have an effect on the beta-endorphin receptors. Nevertheless, the risk of dependency when taken chronically limits their use to short time periods.(11) Medications that function as topical anesthetics, such as combinations of lidocaine and prilocaine or s-cream, are also approved for the use of premature ejaculation. Nonetheless, since they have a high transfer rate the use of prophylactics is recommended. (11,12)

Finally, sexual education is provided by psychosexual therapy in order to dispel sexual myths, acquire confidence, control anxiety and reeducate behaviors related to sexual relations. The different therapies have shown good results, although they are much more effective when pharmacological and psychological therapies are combined. (13,14)

Neuromodulation of the posterior tibial nerve

Peripheral neuromodulation is defined as any technique aimed at indirectly stimulating the neurological roots responsible for the motor and/or sensorial functioning of a particular organ, viscera and/or support structures. Neuromodulation of the posterior tibial nerve arose from the advances in these techniques. It has typically been performed by using a needle electrode to electrically stimulate the posterior tibial point, though a surface electrode can be used as an alternative technique. (15)

Neuromodulation of the posterior tibial and the pudendal nerves is primarily described for the treatment of pelvic floor pathologies, and neuromodulation of the posterior tibial is approved by the FDA to treat urinary incontinence when physiotherapeutic or pharmacological treatments are insufficient. (16,17)

At the physiological and anatomical levels, the micturition and ejaculatory reflexes share areas in common, which are described below. In the case of micturition, the *parasympathetic reflex arc* is the basis of this process. The detrusor muscle and the free nerve endings are stimulated by the distention of the bladder. When it fills with urine, the sensation passes through the pelvic nerve (sacral roots S2-S3 and S4) and then ascends through the medulla until reaching the neuron in the pontine micturition center (PMC) and the cerebral cortex, where the propioceptive stimulus is converted into the desire to urinate. This can be inhibited in the brain, the basal ganglia, and the cortex itself which acts retrogradely on the PMC. This *parasympathetic reflex arc* descends until reaching the motor neuron at the sacral level (S2-S3 and S4) where it exits through the pelvic nerve until it reaches the bladder's perivesical and intramural parasympathetic ganglia, initiating the contraction of the detrusor muscle and producing micturition. The sympathetic micturition reflex arc is mediated by the hypogastric nerve which contains sensitive fibers that extend to the medulla at the level D9 to L1 and exit through the same hypogastric nerves, reaching the bladder and the urethra and producing the relaxation of the bladder's detrusor muscle and the contraction of the vesical neck, preventing micturition.

With regard to ejaculation, this has a neurological control which also depends on the synchrony of the sympathetic and parasympathetic systems, and which participate in this process synergistically. For study purposes, ejaculation is divided into two stages: emission and expulsion.

The emission stage is characterized by the mixing of fluids from the seminal glands, the prostate and the bulbourethral glands. These fluids accumulate in the prostatic urethra since the system of internal and external sphincters are closed, creating a high pressure chamber. This stage is regulated by the lumbar dorsal (D12-L2) sympathetic system. The expulsion stage is characterized by an increase in pressure in the chamber behind the prostatic urethra. This increased pressure from the rhythmic contractions of the perineal muscles, and from the urethra itself, produces the expulsion of the fluids accumulated there. This stage is controlled by the *sacral parasympathetic system* (S2-S3 and S4).

The stimuli produced in the genital area also ascend through the medulla until reaching the regions of the thalamus and the cerebral cortex where the reflex is regulated, and where the

neurotransmitters play a key role, particularly in serotonin levels, among many other functions. (18)

The posterior tibial nerve is a mixed (sensor and motor) nerve. It contains fibers that have medullary origins in the sacral plexus, as does the innervation of the structures of the pelvic floor. Thus our hypothesis is that retrogradely stimulating it with TPTNS (Transcutaneous Posterior Tibial Nerve Stimulation) will have an effect on the anatomical structures that depend on it, such as the musculature of the pelvic floor and its neighboring structures, the urethra, prostate and seminal glands. The stimulation of the posterior tibial nerve produces the inhibition of the parasympathetic stimulus, thereby affecting ejaculation.

Evidence Related to Posterior Tibial Neuromodulation for Urinary Incontinence and Pelvic Pain

A variety of studies have evaluated the efficacy and safety of neuromodulation of the posterior tibial to treat urinary incontinence and pelvic pain. Four systematic reviews of this technology have been found. Since they repeated studies and results, the most recent and best quality studies are presented below.

In a systematic review published in 2012 of two randomized clinical studies with high-quality methodologies, a significant decrease in urinary frequency and urge urinary incontinence was demonstrated in patients treated with electrostimulation of the posterior tibial, compared to a placebo group. One of these studies also reported significant improvement in nocturia and urinary urgency. In another clinical trial with a high-quality methodology, no differences were observed in urinary frequency when comparing electrostimulation and Tolterodine. (19)

Bieman et. al. evaluated the effectiveness of electrostimulation for different indications, including urinary incontinence, fecal incontinence and chronic abdominal pain. This review found 5 randomized clinical trials, with small sample sizes and poor methodological quality, that suggested improvements in the symptoms associated with hyperactive bladder, frequency, urgency, nocturia and urinary incontinence (range 36.7 - 80%). With regard to symptoms related to fecal incontinence, another study included in this review found a 53% decrease for the patients who were included. And to treat pain, another clinical trial reported that chronic pelvic pain decreased in 40% of patients. None of the studies reported serious adverse events. (20)

The most recent and long-term findings from a clinical trial show favorable results with respect to frequency, episodes of urge incontinence, nocturia and episodes of moderate to severe urgency 5, 12, 18 and 24 months after finishing treatment. (21)

JUSTIFICATION

Premature ejaculation is a condition which affects roughly 25% of the male population, creating problems in their sexual life and affecting their quality of life. (1)

Although a variety of pharmacological and therapeutic treatments exist today, they have several drawbacks that limit their long-term use, such as: undesirable secondary effects from tricyclic antidepressants and selective and non-selective serotonin reuptake inhibitors, risk of dependence with the chronic use of opioid analgesics and a high transfer rate with topical anesthetics which requires the use of condoms. (10-12)

Given the results obtained from using posterior tibial neurostimulation for several pelvic pathologies, including urge incontinence and some reported cases of chronic pelvic pain, and considering the physiology and anatomy of these structures, it is feasible that the use of this therapy for patients with primary premature ejaculation will have beneficial effects. There are three reasons for this: 1) The parasympathetic reflex is inhibited, primarily affecting the expulsion stage of ejaculation; 2) Since these stages are regulated by the autonomic nervous system and are linked with it, a sympathetic effect on emission could be achieved, generating a global delay in the start of the ejaculatory reflex; 3) Since ejaculation is also controlled at the supraspinal level, and considering studies of urinary incontinence performed by Finazzi-Agro (22) which show evidence of changes in evoked potential produced at the frontal cortex level after stimulating the posterior tibial nerve, suggesting changes at the cortex level and explaining the long-term control of incontinence, if our hypothesis is correct we could expect to see a change not only during the percutaneous electrostimulation of the posterior tibial nerve but it could also be prolonged over time.

The present study will make it possible to identify whether neurostimulation of the posterior tibial is beneficial for patients with premature ejaculation, as well as to determine the risks associated with this therapy. This evidence will serve as a basis for subsequent comparative studies to evaluate the best treatment options, thereby providing an opportunity to offer patients more treatment options, possibilities and alternatives to complement or substitute current treatments.

OBJECTIVES

Primary

Evaluate the efficacy of transcutaneous electrostimulation of the posterior tibial nerve on the ejaculatory reflex.

Secondary

- Measure changes in ejaculation time during and after the stimulation of the posterior tibial nerve, based on the PEDT (Premature Ejaculation Diagnostic Tool) and IELT (intravaginal ejaculation latency time).
- Evaluate the secondary or adverse effects of this therapy on the quality of the erection using the IIFE5 and EHS.
- Quantify secondary or adverse sexual effects from transcutaneous posterior tibial nerve stimulation.
- Determine the appropriate therapy time for the administration of posterior tibial electrostimulation for ejaculation control.

RESEARCH HYPOTHESIS

Null hypothesis: No clinically significant improvement in ejaculation time exists for patients who are treated with Transcutaneous Posterior Tibial Nerve Stimulation (TPTNS)

Alternative hypothesis: Clinically significant improvement in ejaculation time exists for patients who are treated with Transcutaneous Posterior Tibial Nerve Stimulation (TPTNS).

MATERIALS AND METHODS

Type of Study
Phase II Clinical Trial

Study Population
Patients who have been admitted to the Boston Medical Group clinics in Bogota and have been diagnosed with primary premature ejaculation and have not received treatment over the last six months.

Sample
Patients in the study population who meet the following selection criteria:

Inclusion criteria
- Over 18 years of age and less than 50 years of age with no cardiovascular risk factor other than age.
- Having been diagnosed with primary premature ejaculation according to the American Psychiatric Society's DSM 5 Diagnostic and Statistical Manual.
- Agreeing to participate and providing signed informed consent.
- Stable relationship for over 6 months, with frequent intercourse at least once per week.

Exclusion criteria:
- Diagnosis of erectile dysfunction according to the IIFE 5 (score under 21).
- A PEDT score under 8.
- Use of treatment for premature ejaculation during the study or over the 6 months prior to beginning the study.
- Use of pacemaker or heart defibrillator.
- Epilepsy or convulsions
- Venous insufficiency (varices) or cutaneous wounds or injuries on the lower extremities.
- Congenital or acquired anatomical abnormalities of the penis.
- Taking medications that affect ejaculation control, including psychiatric medications, opioid analgesics and medications for pathologies of the prostate such as alpha blockers.
- Psychological or psychiatric disorders that prevent the patient from undergoing the treatment or recording the measurements as established.
- Difficulty going to the clinic 3 times per week as required by the protocol.
- Patients with precoital premature ejaculation.
- Use of barrier contraceptive methods or local anesthetics.

Sample size
The "single stage procedure" proposed by Fleming was used to estimate the sample size for this type of trial. For P0=10% and P1=30% with an alpha error of 5% and a beta of 80%, 18 patients need to be included in order to prove the study's hypothesis. After adjusting this number by a percentage of loss of 30%, which is observed in daily practice, 24 patients will be included in the study.

Sample
A consecutive, non-probabilistic sample will be performed. The participants will be included sequentially as they are admitted to the clinic, with their voluntary agreement to participate in the study.

OUTCOMES

Primary Outcome

Proportion of patients with clinical improvement of premature ejaculation, defined as a tripling of the baseline time (without treatment), as measured by the IELT (intravaginal ejaculation latency time) during the therapy and three months after completion.

Secondary Outcomes

The patient presents a change in the PDET score.

The magnitude of the change in the PEDT score.

Type, frequency and severity of adverse events during the therapy.

OUTCOME VARIABLES

Since the aim is to evaluate possible changes in the length of time of the appearance of the ejaculatory reflex, two tools will be used to quantify this datum: the PDET and IELT (Appendix 1). The first is a questionnaire that evaluates the perception the patient has of his situation, and the second will be measured with a timer which the patient will use to document the time it takes between vaginal penetration and the appearance of ejaculation, data which must be recorded on the in-home chart (Appendix 2) which each patient will have and which he must bring to each follow-up appointment. These data will be used to quantify the following variables:

- IELT and PEDT at week 6 of the protocol (halfway point).
- IELT and PEDT at the end of treatment.
- IELT and PEDT three months after finishing the protocol.

Other variables of interest

Variable	**Conceptual Definition**	**Operational Definition**	**Measurement Scale**
Age	Time between birth and the interview date	Number of years completed	Quantitative

Frequency of sexual relations	Number of sexual relations in one week	Number of relations per week	Quantitative
Alcohol consumption	Frequency and amount of alcoholic beverages consumed	0. Occasional 1. Frequent	Qualitative
Consumption of psychoactive drugs	Natural or synthetic chemical substances that affect the central nervous system when consumed.	1. Psycho-depressants 2. Psycho-stimulants 3. Cannabis 4. Opiates 5. Opioids 6. Volatile.	Nominal Qualitative
Baseline IELT	Average intravaginal latency time before beginning therapy, based on measurements taken during two weeks prior to beginning treatment	Seconds	Quantitative
Baseline PEDT	Score from the premature ejaculation diagnostic scale before beginning treatment	Score from 0 to 20	Quantitative

Data Analysis Plan

A descriptive analysis will be performed of the sociodemographic and clinical characteristics of the research subjects. For the categorical variables, absolute and relative frequencies will be estimated. For the numerical variables, central tendency and dispersion measurements will be estimated.

To evaluate the efficacy of this new therapy, the proportion of patients whose illness improves will be estimated and compared with the expected proportion proposed by the hypothesis (30%). Improvement is defined as the tripling of the baseline (without treatment) intravaginal latency time.

The safety will be evaluated by estimating the incidence of adverse events experienced by the patients during the study. These will be classified by the degree of severity according to WHO criteria.

The analyses will be performed with Stata 14.

Data Collection and Processing Techniques and Procedures

The patients are admitted to the clinic where they receive a medical evaluation in which they are diagnosed as patients with primary PE. Once this occurs, they are invited to participate in the study by their own voluntary choice. If the patient is interested in participating, the informed consent process is conducted and the corresponding document is signed. Then, an informational email is sent to the telephone center staff responsible for investigations, so that the information required from the patient is inputted into the corresponding database for the purpose of following-up on all of the therapy and follow-up appointments.

Prior to receiving therapy, the patient will perform a two-week process in which he will measure the intravaginal latency time with a digital timer or stopwatch APP and record it on the in-home chart. This has two objectives: first, the patient adapts to the way in which he will measure this time when having sexual relations during the study; second, to have a more precise reference point for the initial IELT, which will be used as a baseline to demonstrate changes during the study protocol.

The therapy will be conducted as follows: Three (3) sessions per week for twelve (12) consecutive weeks, with a duration of 30 minutes each, with the application of 20 Hertz with a pulse amplitude of 200 MI sec. in each session. The intensity will be applied individually for each patient depending on the tolerance of the individual. In each session, it is normal to have plantar flexion of the foot and flexion of the first toe, and after the session and particularly during the first sessions there is the possibility of muscle pain, which should be tolerable. Appendices 3 and 4 provide a more detailed description of the scheme and procedure.

During the study, each patient will have an in-home chart which he must fill out after each sexual encounter and bring to each appointment. The patients will be given strict telephone follow-up calls aimed at their keeping their monthly follow-up appointments, or if not possible due to lack of time a virtual appointment will be conducted by the physician using skype or by telephone.

It is essential that each patient who is admitted into the study complies with the scheduled electrostimulation sessions. If one of the protocols is broken, the patient will be treated as a loss to follow-up since his information could be incorrect.

PEDT and IELT measurements will be taken at the beginning of therapy, at the halfway point, upon finishing the protocol and three months after completion.

All of the information will be recorded in the electronic clinical chart that is already in use at the Boston Medical Group. All of the clinical data will be stored in a flat Excel database. Upon completing the collection of the entire sample, the clinical information that is lacking will be extracted from the electronic clinical chart. This information will be exported to a flat file to be read later by a statistical package.

EXPECTED IMPACT

By determining the efficacy and safety of TPTNS (transcutaneous posterior tibial nerve stimulation) for treating premature ejaculation, it will be possible to conduct a comparative evaluation and thereafter implement new therapies to treat this condition, benefiting patients by having different treatment options to offer.

In terms of generating knowledge, two presentations are planned at national and/or international urology conferences or conferences related to the treatment of male sexual pathology. At least one article presenting information about the results from the study will be published in an international indexed journal.

ETHICAL ASPECTS

The research will comply with the legal and ethical guidelines described by 1993 Resolution No. 8430 established by the Colombia Ministry of Health and other national regulations. The principles developed by the World Medical Association for research involving human subjects, as stated in the Declaration of Helsinki, will be respected and complied with as will the ethical guidelines by the Council for International Organizations of Medical Sciences (CIOMS) and the Belmont Report.

The intervention to be evaluated has been proven to be effective for other conditions having a similar physiopathology, and the published reports of scientific evidence show that the rate of adverse events is very near zero or zero. The intervention will be administered by personnel who have all of the technical skills and experience required to administer the intervention as well as to treat possible adverse events.

According to Article 11 of The Ministry of Health's 1993 Resolution No. 8430, the risk associated with the present research is considered to be higher than the minimum. In compliance with this legislation, approval will be requested from the Ethics Committee for the authorization of the development of this investigation.

Each subject will be informed of all of the possible consequences from participating in this investigation (regardless of their probability of occurrence). Informed consent will be explained and obtained, and the individual will be entirely free to decline to participate in the study without this decision having any affect on the medical care for his illness.

In addition, to address the need to protect the privacy of each research subject and his partner an instructional guide will be made available for the confidential handling of the information collected. The confidentiality of the subjects will be ensured and, therefore, the databases will be housed in the Boston Medical Group's offices and only the study's researchers will have access to them.

Lastly, the study will ensure that the researchers possess the technical competency required for conducting this study and that they have the tools needed to manage and use the research data.

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APPENDIX. INFORMED CONSENT

Date: dd/mm/year

Title of the investigation: *TRANSCUTANEOUS POSTERIOR TIBIAL NERVE STIMULATION (TPTNS) FOR TREATING PATIENTS WITH PREMATURE EJACULATION PHASE II CLINICAL TRIAL*

Place: Boston Medical Group Clinic, Calle 97.
Principal Researcher: Olga Lucía Uribe
Telephone number: 3006827931
Duration of the study: 12 months
Approved by: Research Ethics Committee, Instituto de Bioética Pontificia Universidad Javeriana
Ethics Committee contact: Dr. Efraín Méndez. Email: bioetica@javeriana.edu.co Telephone: 320 8320 Ext. 4537 - 38

Dear Sir,

You are at this moment about to enter a phase II clinical trial designed by the Colombia Boston Medical Group, whose objective is to evaluate whether transcutaneous posterior tibial nerve stimulation increases ejaculation time in men with premature ejaculation.

This study is being conducted because we have a theory that this type of therapy delays ejaculation time, given that this therapy has been demonstrated to be effective for the control of urinary incontinence, without producing adverse events, and the structure and functioning of these organs are similar to those involved in ejaculation.

The procedure is completely experimental and will be conducted over 12 weeks with a frequency of 3 times per week, as follows:

1. With the patient lying down on his back, with no shoes or socks, the area to be treated is cleaned with a gauze moistened with a little alcohol.
2. The distance is then measured from the tip of the active electrode (black cathode) to 3 – 5 cm above the inner ankle and 1 cm behind the tibia.
3. The second reference electrode (red anode) is adhered onto the heel.
4. The therapy uses a continuous current with a frequency of 20 Hz and pulse width of 200 uS for 30 minutes, and an intensity that is tolerable for the patient.
5. When the application time is completed, the adhesive electrodes are removed from the patient's skin.

Although no formal reports exist of adverse effects from posterior tibial nerve electrostimulation, you could possibly present an allergic reaction to the electrodes' adhesive, a sensation of transient paresthesia in the lower extremity, urinary retention or constipation.

The possible benefits that could be obtained with this therapy is an increase in ejaculation time, and with that, an improvement in the quality of your sexual life.

It is important to mention that whenever needed, we will clarify and answer any questions or concerns that you have about the procedures, risks, benefits and other issues related to this study and the treatment that you will receive. The entire design and application of this study is supervised and approved by the Research Ethics Committee of the Instituto de Bioética de la Pontifica Universidad Javeriana.

With respect to the information used by the study, the data associated with both you and your partner will be handled in a confidential manner and, therefore, only the study's researchers will have access to them. The results obtained will be published in medical-scientific journals and will be reported as group data without identifying the patients or revealing any of the participants' personal data.

In the event that damage is caused by the investigation, the Boston Medical Group will provide the respective medical treatment and the indemnities to which you have a legal right.

By signing this document, you authorize your inclusion in the study group. You are free to withdraw from this at any time during the investigation and this decision will not have any detrimental effect on the treatments recommended by your physician.

All of the patients included must completely fill out the questionnaires and must show up for all of the scheduled sessions and subsequent follow-up appointments. If you miss a session or do not provide the information required, this will result in your exclusion from the study with no detrimental effect on other treatments recommended by your physician.

SIGNATURE OF THE PARTICIPANT

I _____, identified by _____ number _____, _____. I agree to my inclusion in the study mentioned and the inclusion of my information.

_____

Patient signature.
CC:_____

WITNESS 1:
Name:_____
CC:_____

Signature: _____

WITNESS 2:
Name:_____
CC:_____

Signature: _____